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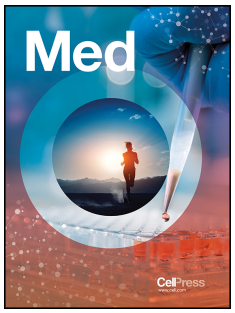

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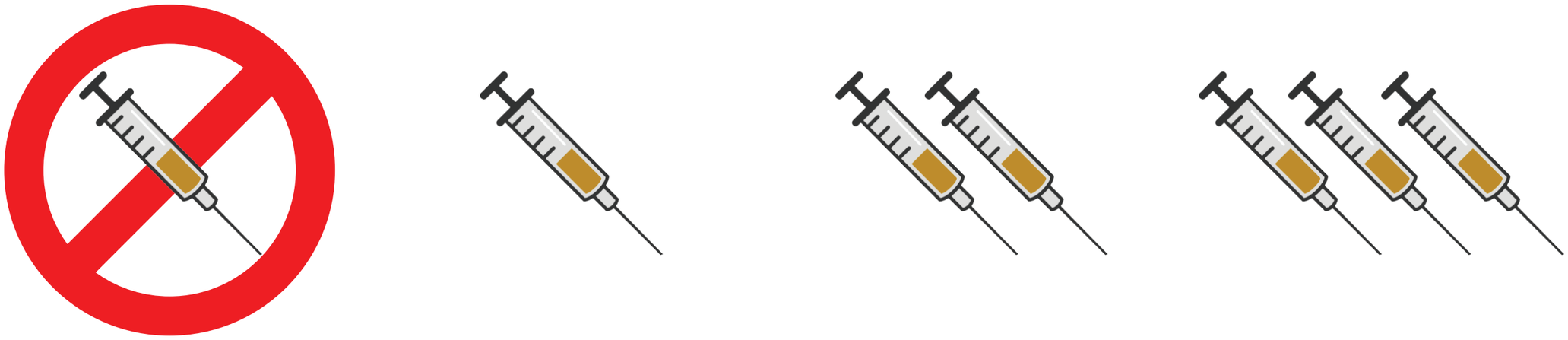
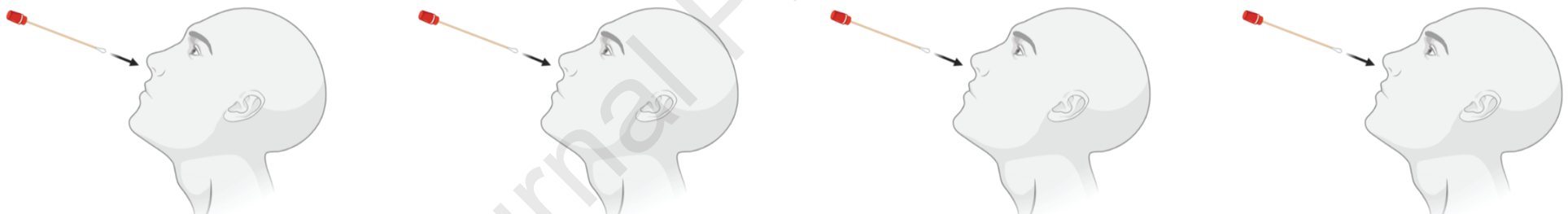
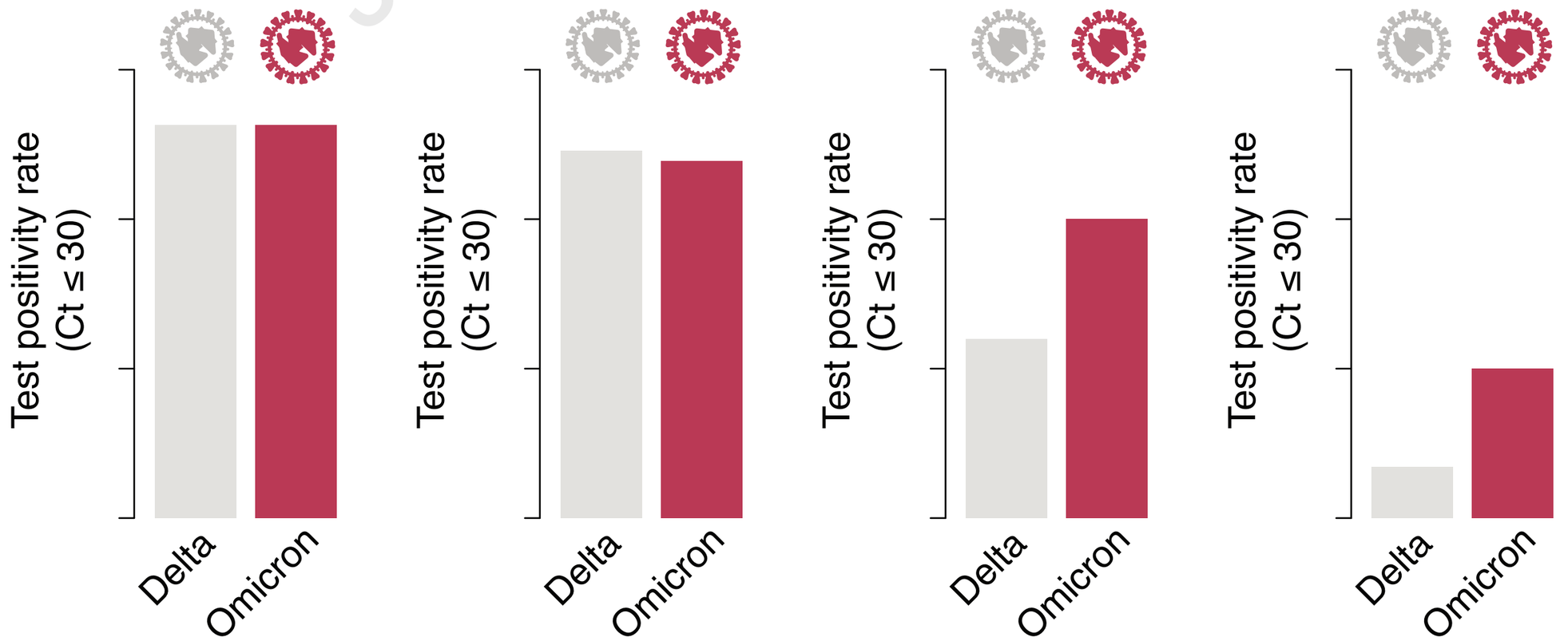
COVID-19 vaccination



PCR test



Test positivity rate



Rapid emergence of SARS-CoV-2 Omicron variant is associated with an infection advantage over Delta in vaccinated persons

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Summary

Background

The SARS-CoV-2 Omicron variant became a global concern due to its rapid spread and displacement of the dominant Delta variant. We hypothesized that part of Omicron's rapid rise was based on its increased ability to cause infections in persons that are vaccinated compared to Delta.

Methods

We analyzed nasal swab PCR tests for samples collected between 12-26 December 2021 in Connecticut when the proportion of Delta and Omicron variants were relatively equal. We used the spike gene target failure (SGTF) to classify probable Delta and Omicron infections. We fitted an exponential curve to the estimated infections to determine the doubling times for each variant. We compared the test positivity rates for each variant by vaccination status, number of doses, and vaccine manufacturer. Generalized linear models were used to assess factors associated with odds of infection with each variant among persons testing positive for SARS-CoV-2.

Findings

For infections with high virus copies (Ct < 30) among vaccinated persons, we found higher odds that they were infected with Omicron compared to Delta, and that the odds increased with increased number of vaccine doses. Compared to unvaccinated persons, we found significant reduction in Delta positivity rates after two (43.4-49.1%) and three vaccine doses (81.1%), while we only found a significant reduction in Omicron positivity rates after three doses (62.3%).

Conclusion

The rapid rise in Omicron infections was likely driven by Omicron's escape from vaccine-induced immunity.

Funding

This work was supported by the Centers for Disease Control and Prevention (CDC).

Key words

SARS-CoV-2; Omicron; Delta; COVID-19 vaccines; epidemiology; genomic surveillance

Introduction

The emergence of SARS-CoV-2 variants continues to shape the COVID-19 pandemic[1]. The success of the Alpha (lineage B.1.1.7) and Delta (B.1.617.2) variants that dominated the pandemic for most of 2021 was primarily driven by successive increases to their intrinsic transmissibility. As population immunity to SARS-CoV-2 increases through infections and vaccination, selection for variants that are partially resistant to the immune response, in particular neutralizing antibodies, should also increase[2]. Mathematical modeling suggests that SARS-CoV-2 variants with increased transmissibility and partial immune escape may significantly increase infections even in a well-immunized population[3]. A variant with these properties could significantly limit vaccine effectiveness against infections and lead to a new "wave" of COVID-19 cases.

The detection and rapid spread of the SARS-CoV-2 Omicron variant (B.1.1.529) in Botswana and South Africa grew as a global concern because it contained 15 mutations in the spike protein immunogenic receptor binding domain[4,5]. Subsequent *in vitro* assays showed that antibody-mediated neutralization using sera derived from vaccinees was significantly lower for Omicron than the previously dominant Delta variant[6–11]. For example, serum antibody neutralization from mRNA-1273 vaccinees within 3 months of the second vaccine dose was diminished 43x with Omicron compared to Delta and from BNT162b was diminished 122x[12]. However, neutralization against Omicron was significantly enhanced after a booster vaccine dose, including for Ad26.COV2.S[12,13]. While these data suggest that Omicron may have an infection advantage over Delta in vaccinated persons, *in vitro* neutralization is not a direct correlate for human protection from infection.

The emergence of Omicron led to record-setting levels of COVID-19 cases in many parts of the world, even in well vaccinated regions[4,14–17]. Using a population in southern Connecticut, USA in which 48.5% have received at least one vaccine dose (including children and adults), we tested the hypothesis that the rapid increase in Omicron infections was at least partially influenced by its ability to cause infections in persons that are vaccinated compared with Delta. We established a surveillance system to differentiate Delta and Omicron cases using PCR and genome sequencing, and selected a period in mid-December

2021 for the study when Delta and Omicron were relatively equal. From this period, we analyzed 37,877 nasal swab PCR test results and compared the Delta and Omicron positivity rates by the number of vaccine doses received. We confirmed our results using a logistic regression model to calculate the odds of detecting Omicron relative to Delta among infected persons and further assessed the effect of the number of COVID-19 vaccine doses and vaccine manufacturer (Ad26.COV2.S, mRNA-1273, or BNT162b2). We found that three vaccine doses were required to reduce Omicron positivity rates in our population, and that Omicron has an infection advantage in vaccinated persons relative to Delta that is proportional to the number of vaccine doses.

Results

Rapid emergence of Omicron

In late November, 2021, we established a surveillance program in southern Connecticut, USA to investigate the emergence of Omicron. At that time, BA.1 (also known as B.1.1.529.1) was the primary Omicron lineage spreading globally. Similar to the Alpha variant, Omicron BA.1 has a spike gene deletion (Δ69/70 HV) that causes "spike gene target failure" (SGTF) when using the ThermoFisher TaqPath COVID-19 Combo Kit qRT-PCR assay, allowing us to quickly identify potential Omicron infections. Yale New Haven Health (YNHH) uses TaqPath for testing mid-turbinate nasal swabs from symptomatic and asymptomatic outpatients for SARS-CoV-2 at collection sites in southern Connecticut. Our SGTF case definition included having an ORF1ab gene target PCR cycle threshold (Ct) of < 30 and spike gene target "not detected". We retrospectively applied the SGTF case definition to a cross-sectional study of samples collected since 15 November 2021 and prospectively to 10 January 2022 (**Figure 1A**).

We detected the first sample meeting our SGTF case definition on 4 December 2021, which we sequence-confirmed as Omicron lineage BA.1. We sequenced a subset of samples collected from 22 November to 27 December (*n* = 695), and 100% (216/216) of the SGTF samples were confirmed as Omicron (BA.1) and 100% (479/479) of samples without SGTF (i.e., the spike gene was detected) were confirmed as Delta (B.1.617.2 or AY.x; **Data S1**). This established our case definitions as adequate proxies for Omicron (BA.1) and Delta infections during our study period.

We found that Omicron became the dominant variant in our population 16 days after its first detection (20 December 2021; **Figure 1A**). Fitting an exponential curve to cumulative cases, we estimated that Omicron cases doubled every 3.1 days (95% confidence interval (CI): 2.8-3.4), 4.3x shorter than the initial doubling time for Delta during its emergence period from 18 April to 29 July, 2021 (13.4 days [95% CI: 12.5-14.5]; **Figure S1A-C**). The rapid emergence of Omicron in southern Connecticut was also associated with a rapid rise in COVID-19 cases (**Figure 1a**), as seen in many places around the world. When we first detected Omicron, the US Centers for Disease Control and Prevention estimated that 71-74% of the population in southern Connecticut had completed a primary COVID-19 vaccine series (1 dose of Ad26.COV2.S or 2 doses of mRNA-1273 or BNT162b2)[18]. Therefore, we hypothesized that part of the rapid increase in Omicron infections stemmed from its increased ability to cause infections in persons that are vaccinated compared with Delta.

Omicron versus Delta in vaccinated persons

To investigate if Omicron is more likely than Delta to cause infections in vaccinated persons, we analyzed 37,877 nasal swab PCR tests conducted from 12-26 December when the total number of probable Delta

and Omicron infections were relatively equal (Delta = 1374/2761, 49.8%; Omicron = 1387/2761, 50.2%; **Figure 1A**, **Figure S2**). We conducted a medical records review to identify that the 37,877 tests during that period were from 33,416 unique persons with known vaccination status. Since some individuals tested multiple times during the study period, only the first test was included. For each PCR test, we collected information on age and sex of the person tested, test date, test outcome (negative, positive > 30 Ct, positive ≤ 30 Ct Delta, and positive ≤ 30 Ct Omicron; **Figure S2**), and date and manufacturer of each COVID-19 vaccine administered (Ad26.COV2.S, mRNA-1273, and/or BNT162b2). We excluded persons who indicated in their records a preference to opt out of research and the number of doses was regarded as those taken at least 14 days before the SARS-CoV-2 test. In our population (including children and adults), 53.6% were unvaccinated, 46.4% received at least one vaccine dose, 42.2% received at least two vaccine doses, and 7.5% received three vaccine doses. Additional details regarding the characteristics of the population are provided in **Table 1**.

We then calculated the ≤ 30 Ct test positivity rates for each variant stratified by vaccination status (**Figure 1B**, **Table 2**). We found that the positivity rate among unvaccinated persons was higher for Delta than Omicron (5.3% [95% CI: 5.0-5.7%] vs. 4.4% [95% CI: 4.1-4.7%], $P<0.0001$). We found similar results in persons who received a single vaccine dose. Conversely, our results show that Omicron had higher positivity rates than Delta among those who received two doses within five months (Omicron: 4.2% [95% CI: 3.8%-4.6% vs. Delta: 3% [95% CI: 2.6-3.3%], $P<0.0001$), two doses more than five months ago (Omicron: 4.2% [95% CI: 3.8-4.6%] vs. Delta: 2.7% [95% CI: 1.8-3.6%], $P=0.007$), and three vaccine doses (Omicron: 2% [95% CI: 1.4-2.5%] vs. Delta: 1.0% [95% CI: 0.6-1.3%], $P=0.04$). Our estimates of Omicron positivity rates in persons receiving one or two vaccine doses were not significantly lower than unvaccinated persons but were 49.7% lower after three doses. In comparison, the reduction in Delta positivity rates from unvaccinated to two vaccine doses was 45.6-49.6% and to three vaccine doses was 83.2% (**Table S2**). Despite the higher positivity rates for Omicron in vaccinated persons, we still found that 57.2% (793/1387) of the Omicron infections in our population occurred in persons who were unvaccinated and 96.3% (1336/1387) were eligible for one or more vaccine doses at the time of PCR testing.

We confirmed our ≤ 30 Ct test positivity analysis by calculating the odds of detecting Omicron relative to Delta using a logistic regression model (**Figure 1C**, **Table S1**, **Table S2**). We used the first SARS-CoV-2 test in the logistic regression model as some persons were tested multiple times. For infections among persons who were vaccinated, we found higher odds that they were infected with Omicron (versus Delta), and that the odds appeared to increase with increased number of vaccine doses (1 dose odds ratio [OR] = 1.3 [95% CI: 1.8-2.0]; 2 doses ≥5 months OR = 2.3 [95% CI:1.5-3.7]; 2 doses <5 months OR = 1.9 [95% CI: 1.5-2.2]; 3 doses OR = 3.0 [95% CI: 1.8-4.9]). The odds of infection did not vary by sex or age and our results were similar when we stratified the data by Ad26.COV2.S, mRNA-1273, or BNT162b2 (Figure S2). These findings support our hypothesis that Omicron has an infection advantage in vaccinated persons relative to Delta.

PCR cycle thresholds by variant and vaccination status

Next, we sought to determine if infection advantage for Omicron relative to Delta in vaccinated persons (**Figure 1**) was related to virus copies in the nasal passage. We compared the mean nasal swab PCR Ct values by variant category (Omicron or Delta) and stratified by the number of vaccine doses received (**Figure 2A**). Lower PCR Ct values correspond to higher virus copies. Combining positive tests from unvaccinated and vaccinated persons, we found that the overall mean PCR Ct values were higher for infections with Omicron than Delta (Omicron = 20.96 [95% CI: 12.70-29.21] vs. Delta = 20.68 [95% CI:

11.02-30.34], *P*<0.001, Kruskal-Wallis test; **Figure 2A,B**). Similarly, the PCR Ct values were consistently lower Omicron compared to Delta across all vaccination categories in our population, although we only found statistically significant differences in persons vaccinated with two doses (Omicron = 21.19 [95% CI: 12.67-29.71] vs. Delta = 20.62 [95% CI: 11.10-30.14], *P*= 0.049; **Figure 2A,B**).

To adjust for age, sex, vaccine doses, and vaccine manufacturers, we compared nasal swab PCR Ct values of Omicron relative to Delta by fitting a regression model with a Gaussian family distribution. After adjusting for covariates, we found that the PCR Ct values were consistent across vaccine doses, but, confirming our analysis above, Omicron infections had higher Ct values (i.e., lower virus copies) than those infected with Delta (odds ratio=1.55, 95% CI: 1.-2.17; **Figure 2B**, **Table S3**). We found similar trends for the different vaccine manufacturers (**Figure 2C**, **Table S4**). Our results suggest that the enhanced transmissibility of Omicron, and its ability to cause infections in vaccinated persons compared to Delta, is not from higher nasal passage virus copies.

Discussion

We hypothesized that the rapid emergence and spread of the SARS-CoV-2 Omicron variant was partly due to its increased ability to evade immunity from prior infection and/or vaccination. Using a study population seeking outpatient testing when Omicron and Delta were overall relatively equal among infections, we found that Omicron has a relatively higher propensity to cause infections in COVID-19 vaccinated persons. Furthermore, our results show that the advantage of Omicron compared to Delta increases with the number of vaccine doses. While we were not able to study the impact of prior infections, a recent study from South Africa estimated that Omicron had an increased risk of causing SARS-CoV-2 reinfections than the Beta (B.1.351) or Delta variants[14], consistent with our hypothesis. Considering the high vaccination rates and the recent "wave" of Delta infections, the large increase in COVID-19 cases caused by Omicron is likely due in part to a larger population of persons susceptible to Omicron infection that were protected from Delta.

Our findings should not be interpreted as implying that vaccination increases the risk for Omicron infections. On the contrary, vaccination decreased the positivity rates for Omicron and most (57.2%) Omicron infections in our population occurred in persons that were unvaccinated or eligible for a booster dose. Thus, further vaccination would have likely decreased the number of Omicron infections. What our findings imply is that the reductions in infections from vaccination is greater for Delta than Omicron. Compared to unvaccinated persons, we found that *three* vaccine doses were required to significantly reduce the Omicron positive rate (~55% reduction), which was similar to the reduction in Delta positivity rates from *two* doses and significantly lower than the Delta reduction from three doses (~81%). While we did not design this study to directly measure vaccine effectiveness, our results are consistent with vaccine effectiveness studies indicating that a third/booster vaccine dose is needed to significantly reduce Omicron infections[19–24]. To maintain effectiveness against new divergent SARS-CoV-2 variants, the administration schedule for COVID-19 vaccines designed to the original ("Wuhan-Hu-1") SARS-CoV-2 spike gene sequence needs to be continuously evaluated. Overall, this further highlights the need for variant-specific or broad-acting coronavirus vaccines as a long-term solution[25].

We demonstrate that the ability to cause infections in vaccinated persons and increased transmissibility of Omicron compared to Delta is not associated with higher virus copies in the nasal passage. First, our data add further evidence supporting that while vaccination reduces the likelihood of SARS-CoV-2 variants to establish infection, but once infected, vaccination does not significantly reduce virus copies in diagnostic

samples. We show this for both Omicron and Delta, though we previously reported that vaccination can shorten the duration of infection[26]. Second, the increased transmissibility of some previous variants may have been driven by increased viral loads, causing persons to be more infectious[27]. For example, the displacement of Alpha by Delta in mid-2021 was associated with increased virus copies for Delta in diagnostic samples[28,29]. In contrast, the rapid growth rate of Omicron, as shown by our estimates of ~4.3x shorter doubling time compared to Delta, was associated with lower virus copies in nasal swabs (as also shown with anterior nares/oropharyngeal combined swabs[30]). Thus, the increased transmissibility of Omicron relative to Delta may stem from a combination of immune evasion, lower infectious dose, and/or a change in infection tropism to the upper respiratory tract that potentially shortens the generation time and serial interval between infections[16,31–36].

In conclusion, escape from vaccine-induced immunity likely contributed to the rapid rise in Omicron infections. Our findings may also explain why Omicron has been associated with more reinfections[14]. While Omicron was more likely to cause infections in vaccinated persons than Delta, vaccination remains effective in reducing severe disease, even for Omicron[37]. Together with the rebound of vaccine effectiveness after administering a booster dose[21], measures to expand the uptake of the primary vaccine series and additional booster doses remain an important strategy for controlling the COVID-19 pandemic.

Limitations of the study

Our study had several limitations. First, probable Delta and Omicron infections were inferred based on the SGTF PCR data. Although we validated the SGTF results by sequencing a representative number of samples, we could not sequence every positive sample. Moreover, we classified SARS-CoV-2 infections as probable Delta or Omicron only from samples with high virus copies (Ct < 30), which may be biased against Omicron as Omicron infections tend to have higher PCR Ct values than Delta. Second, although our vaccination history data is extensive, our records may not have captured some administrations. We excluded persons with incomplete vaccine information from analysis, but this did not significantly decrease the sample size. Third, we did not have access to data on previous positive test results, serology, or household attack rates, which would have allowed us to study reinfections and variant-specific transmissibility. Fourth, while our data were from outpatients testing for a variety of reasons, including COVID-19 symptoms, or pre-travel, -event, or -procedure, we did not have access to this level of information for each person. Asymptomatic testing for travel or parties increased during the holidays, which can decrease the test positivity rates. However, such changes would not likely introduce a significant bias against either variant. Fourth, the demand for SARS-CoV-2 tests was high during the study period, causing many people to conduct at-home tests or forego testing altogether. Vaccinated persons, especially those who received a booster dose, may have been less likely to seek a PCR test if they were asymptomatic. Since we compare Omicron to Delta by vaccine dose, this change in healthcare-seeking behavior would not likely impact our findings. Fifth, we did not directly assess the effectiveness of COVID-19 vaccines against the Delta and Omicron variants; therefore, any potential implied conclusions regarding the vaccine effectiveness and immunity against these variants should be interpreted with caution. Finally, our study compared the odds of detecting Omicron relative to Delta among infected persons by vaccine administration, our findings should not be erroneously interpreted as vaccination increases the risk for infection with Omicron.

STAR★Methods

RESOURCE AVAILABILITY

Lead contact

Further information and requests for data, resources, and reagents should be directed to and will be fulfilled by the Lead Contact, Nathan D. Grubaugh (nathan.grubaugh@yale.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- The data validating SGTF samples as Omicron lineage BA.1 are located in Data S1. The de-identified and coded PCR and vaccination data are available upon request (requires Data Use Agreement and Institutional Review Board authorization).
- The code used to generate the figures are available at https://github.com/grubaughlab/2022_paper_omicron-v-delta.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Ethics statement

The Institutional Review Board from the Yale University Human Research Protection Program determined that obtaining de-identified test results linked to vaccination status and sequencing of de-identified remnant COVID-19 clinical samples obtained from clinical partners conducted in this study is not research involving human subjects (IRB Protocol ID: 2000031374).

Study participants

Our study consisted of 34,980 unique persons that tested for SARS-CoV-2 (37,877 tests) from outpatient sites, including mass testing locations, in New London, New Haven, and Fairfield Counties, Connecticut, through Yale New Haven Health (YNHH). Provided indications for testing were being symptomatic for COVID-19, exposure to a known case of COVID-19, required testing (e.g. for work, school, or travel), and testing prior to undergoing an aerosol generating procedure. The participants included a diversity of ages from 0-5 to > 60, and 55% were female. We did not obtain information about race or ethnicity. We obtained COVID-19 vaccination information from each person by combining information from the YNHH system's electronic medical records and the Connecticut immunization registry (CT-WiZ), the latter to capture possible out-of-system vaccinations. However, it is possible that some out-of-state vaccinations were missed. The vaccinated persons received Ad26.COV2.S, mRNA-1273, and/or BNT162b2. Details regarding the characteristics of the population are provided in **Table 1**.

Study outcomes

We quantified the positivity rates for the Omicron and Delta SARS-CoV-2 variants in our cross-sectional study, and estimated the odds ratios of detecting Delta in persons testing positive by sex, age, and

vaccination status category. We also calculated the doubling times (in days) for the Omicron and Delta variants to understand their transmissibility. Finally, we assessed the association between the nasal swab PCR Ct value and sex, age, variant, and vaccination status category stratified by vaccine manufacturer.

METHOD DETAILS

PCR testing for variant differentiation

Mid-turbinate nasal swabs from outpatient collection sites were tested for SARS-CoV-2 by the YNHH COVID-19 and Clinical Virology Laboratories using the MagMAX viral/pathogen nucleic acid isolation kit and TaqPath COVID-19 Combo Kit. The TaqPath qRT-PCR assay reports Ct values from three SARS-CoV-2 gene targets: ORF1ab, spike, and nucleocapsid. ORF1ab with Ct values < 30 were investigated for spike gene detection. If the spike gene was detected, the sample was categorized as "probable Delta" and if the spike gene was not detected (i.e., SGTF), the sample was categorized as "probable Omicron".

Sequence confirmation of variants

Mid-turbinate nasal swabs in viral transport media were received from SARS-CoV-2 infections from YNHH. Nucleic acid was extracted from 300 µL of the original sample using the MagMAX viral/pathogen nucleic acid isolation kit, eluting in 75 µl of the elution buffer. The extracted nucleic acid was again tested for SARS-CoV-2 RNA using a "research use only" (RUO) RT-qPCR assay[38], which generates a SGTF result similar to the TaqPath assay. For rapid confirmation of the initial suspected Omicron samples with SGTF, we used the NEBNext ARTIC SARS-CoV-2 Companion Kit and sequenced pooled libraries on the Oxford Nanopore Technologies (ONT) MinION. The standard NEB protocol with PCR Bead Cleanup was slightly modified by using V4 or V4.1 primer pools for amplicon generation, by including an additional bead cleanup step (1:1 beads:sample) after the NEBNext end prep reaction, and by scaling up the barcode ligation reaction by using 16 µL of end-prepped DNA. Final pooled libraries were quantified using the Qubit High Sensitivity dsDNA kit, and the ONT SQK-LSK109 protocol was followed to prime and load the ONT MinION for sequencing. Samples were processed in sets of 14-46 samples with 2 negative controls. The RAMPART application developed by the ARTIC Network was used to monitor the sequencing run until sufficient coverage was reached (https://artic.network/ncov-2019/ncov2019-using-rampart.html)[39]. The ARTIC bioinformatics pipeline was used to generate consensus genomes with fast basecalling done by MinKNOW (https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html). A threshold of 20x coverage was used to call consensus genomes, and negative controls were confirmed to completely consist of Ns.

For routine sequencing of samples with nucleocapsid gene target Ct values ≤ 35, we used the Illumina COVIDSeq Test RUO version. The protocol was slightly modified by using V4 primers for amplicon generation, by lowering the annealing temperature of the amplicon generation step to 63° C, and by shortening the tagmentation step to 3 minutes. Final libraries were pooled and cleaned before quantification with the Qubit High Sensitivity dsDNA kit. The resulting libraries were sequenced using a 2x150 approach on an Illumina NovaSeq at the Yale Center for Genome Analysis. Each sequenced sample had at least 1 million reads. Samples were typically processed in sets of 93 or 94 with negative controls incorporated during the RNA extraction, cDNA synthesis, and amplicon generation steps. The reads were aligned to the Wuhan-Hu-1 reference genomes (GenBank: MN908937.3) using BWA-MEM v.0.7.15[40]. Adaptor sequences were trimmed, primer sequences were masked, and consensus bases were called with simple majority > 60% frequency using iVar v1.3.1[41] and SAMtools v1.7[42]. An ambiguous 'N' was used when fewer than 20 reads were present at a site. In all cases, negative controls were analyzed and confirmed to consist of at least 99% Ns. For both rapid and routine sequencing, Pangolin v.3.1.17[43] was used to assign

lineages[44]. Consensus genomes were submitted to GISAID and included in weekly updates on our website (https://covidtrackerct.com/).

QUANTIFICATION AND STATISTICAL ANALYSIS

Variant growth rates

We calculated daily variant proportions using SGTF samples as a proxy for Omicron and sequence-confirmed lineages for Delta[28] from samples obtained by YNHH. We smoothed these daily variant proportions using a 7-day rolling average. We defined the emergence period for Omicron and Delta as the time since its first sequence-confirmed detection to when the variant reached 95% of total samples in our dataset We defined Delta's emergence period as April 18, 2021 to July 29, 2021 (102 days), and Omicron's emergence period as December 4, 2021 to January 7, 2022 (34 days).We multiplied the daily variant proportions by the daily fitted cases from *Covidestim*[45] for the 3 counties in our study to determine the number of variant cases during the emergence periods. Using these data, we ran a logistic regression analysis for each variant separately, with a sample corresponding to a specific variant category as the binary outcome and the number of days since the first detection of the variant as the predictor. We plotted the smoothed fitted curves for the emergence periods with their 95% confidence intervals (**Figure S1A**), which shows the probability of a given case belonging to a specific variant category over time. We estimated the doubling time by fitting an exponential curve to cumulative cases over time for each variant and dividing log(2) by the resulting coefficient. We show the total fitted cases for each emergence period in **Figure S1B**.

Positivity rates

The PCR positivity rates for each variant were estimated using the ORF1ab Ct values ≤ 30 and SGTF signatures to define as Omicron or Delta. For this analysis, ORF1ab Ct values from 30-40 were included as "negatives" as we could not assign a variant category, and thus the variant-specific positivity rates that we show are not the true overall test positivity rates. We estimated the positivity rates for different SARS-CoV-2 variants as the proportion of persons testing positive during the study period with PCR Ct value <30 for the ORF1ab and S gene targets. To estimate the test positivity by vaccination status, we counted the number of doses received > 14 days before the SARS-CoV-2 test. We calculated the confidence intervals for the proportion based on the standard errors for the binomial distribution. We show each rate with the 95% CI.

Odds of infection with Omicron relative to Delta

To assess the odds of detecting Omicron relative to Delta variant in infected persons, we fitted a logistic regression model to determine the effect of the covariates, namely, sex, age, and vaccination status stratified by the vaccine manufacturer. Similarly, we fitted a generalized linear regression with Gaussian distribution to assess the association between the ORF1ab PCR Ct value with covariates, namely, sex, age, and vaccination status stratified by the vaccine manufacturer. We specified females and unvaccinated persons as the reference categories for the sex and vaccination status covariates in the model. To estimate the odds of infection with Omicron relative to Delta by vaccination status, we counted the number of doses received > 14 days before the SARS-CoV-2 test.

Data S1. Validation of spike gene target failure (SGTF) as proxy for Omicron (BA.1) infection, related to Figure 1. We compared results of our RUO RT-qPCR assay with sequencing results to show that SGTF

is an adequate proxy for detection of Omicron (BA.1) in our study population. We sequenced a subset of samples collected from November 22nd to December 27th. Our N1 threshold was set at Ct ≤30.

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Author contributions

CC, JLW, DMW, WS, CBFV, and NDG conceived the study; AC, RE, DF, NK, FH, HPY, WS, and NDG collected the data and/or samples; CMP, MLL, and DRP supervised the testing labs; MIB, KB, RTK, KP, IMO, JRF, IRT, CC, BDK, CBFV, and NDG performed the sequencing and analysis; CC, AC, RE, JLW, and DMW designed the analysis methods and/or analyzed the data; CCK and NDG wrote the IRB protocol; CC, RE, AMH, CBFV, and NDG drafted the manuscript; All authors reviewed and approved the manuscript; NDG secured funds for the project; WS, CBFV, and NDG supervised the project.

Declaration of interests

NDG is a consultant for Tempus Labs and the National Basketball Association for work related to COVID-19 but is outside the submitted work. All other authors declare no competing interests.

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Figure legends

Figure 1. Variant case counts, test positivity, and odds of infection by vaccination status.
(**A**) Number of persons infected with Delta and Omicron SARS-CoV-2 variants and the proportion of Omicron cases in southern Connecticut. Overlaid on the plot showing the number of positive cases is the proportion of Omicron variants (dots) with a fitted smoothed curve. The growth rate of Omicron compared to Delta during their respective emergence periods is shown in **Figure S1**.
(**B**) The proportion of positive SARS-CoV-2 PCR tests (Ct ≤ 30) for Delta and Omicron variants (using SGTF to differentiate) by vaccination status. The positivity rate values are listed in Table 2.
(**C**) Odds of infection with Omicron relative to Delta variants by age, sex and vaccination status among individuals who tested positive for SARS-CoV-2. We regressed the binary outcome for the SARS-CoV-2 variant (Delta as the reference group) and specified females and unvaccinated persons as the reference categories for the sex and vaccination status predictor variables in the model. Odds ratios > 1 indicate higher odds of detecting Omicron relative to Delta in persons testing positive for SARS-CoV-2 infection. The odds ratio values are listed in **Table S1**. The positivity rates and odds ratios stratified by vaccine manufacturers are shown in **Figure S2** and **Table S2**.

Figure 2. Effect of sex, age, variant and vaccination status on the nasal swab PCR cycle threshold.
(**A**) Nasal swab PCR cycle threshold (Ct) values for the Delta and Omicron SARS-CoV-2 variants by vaccination status.
(**B**) Association of age, sex, and vaccination status with PCR Ct values. The effect sizes > 1 indicate a higher CT value (lower virus RNA) for Omicron compared to Delta, males relative to females, and vaccinated relative unvaccinated persons who received different doses. The odds ratio values are shown in **Table S3**.
(**C**) Association of age, sex, vaccination status, and vaccine manufacturer with PCR Ct values. The odds ratio values are shown in **Table S4**.

Table 1. Demographic characteristics among PCR tests performed between 12-26 December 2021.

Table 2. Positivity rates for Omicron and Delta among PCR tests performed between 12-26 December 2021.

Context and significance

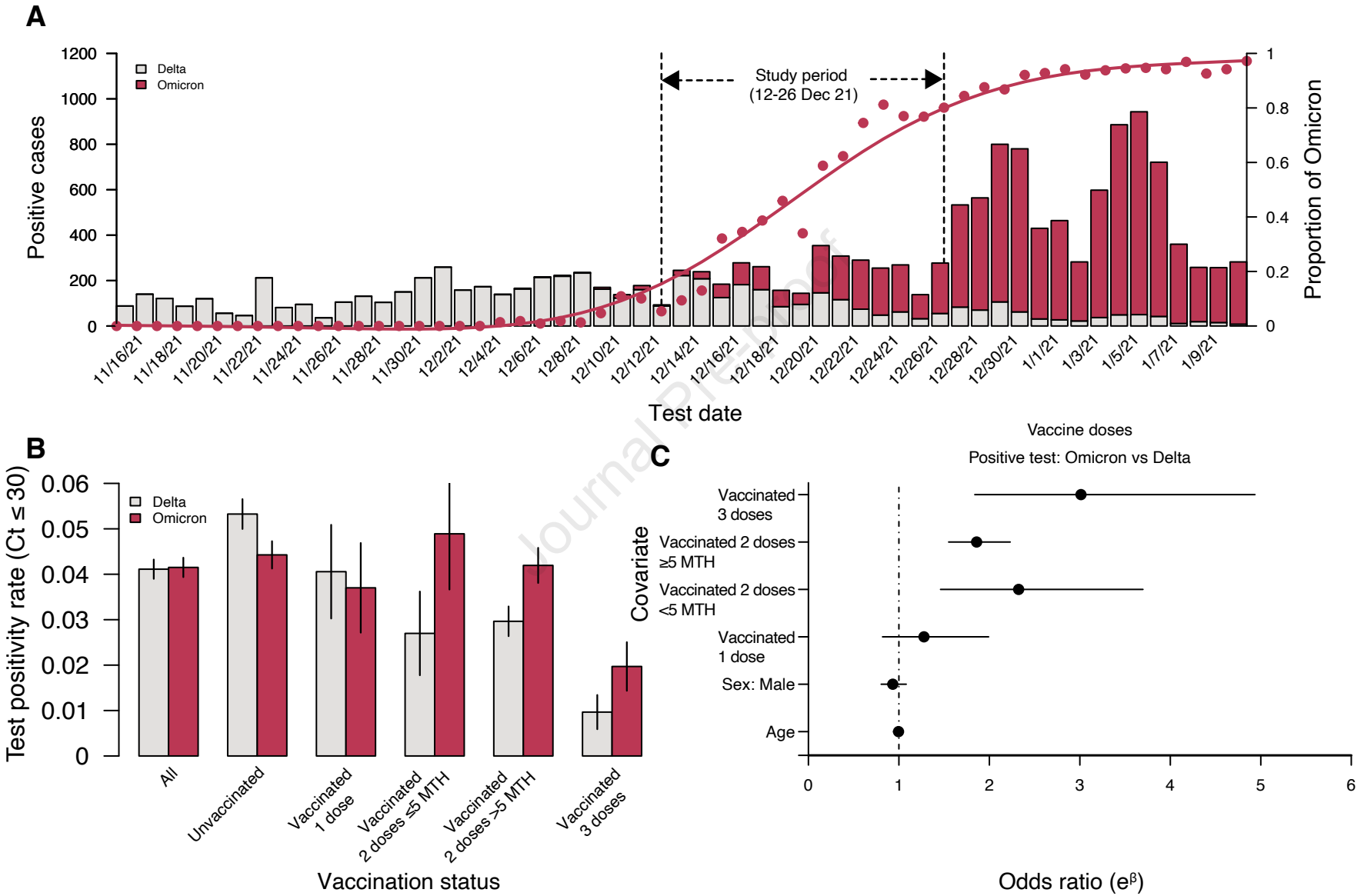
SARS-CoV-2 variants exhibit variable transmissibility and immune escape profiles. Determining these characteristics is critical for new variants to inform measures to minimize the impact of their epidemic waves. Here, cross-sectional investigations of PCR tests differentiating between Delta and Omicron variants from outpatient nasal swabs reveal that the test positivity rates were significantly lower in individuals who received three doses of COVID-19 vaccines than those who were unvaccinated. However, the test positivity rate for Omicron was slightly higher than for Delta among individuals who received a booster dose, suggesting that vaccination is less effective against preventing Omicron infections. These findings highlight the need for increasing uptake of primary COVID-19 vaccine series and booster doses to control the COVID-19 pandemic.

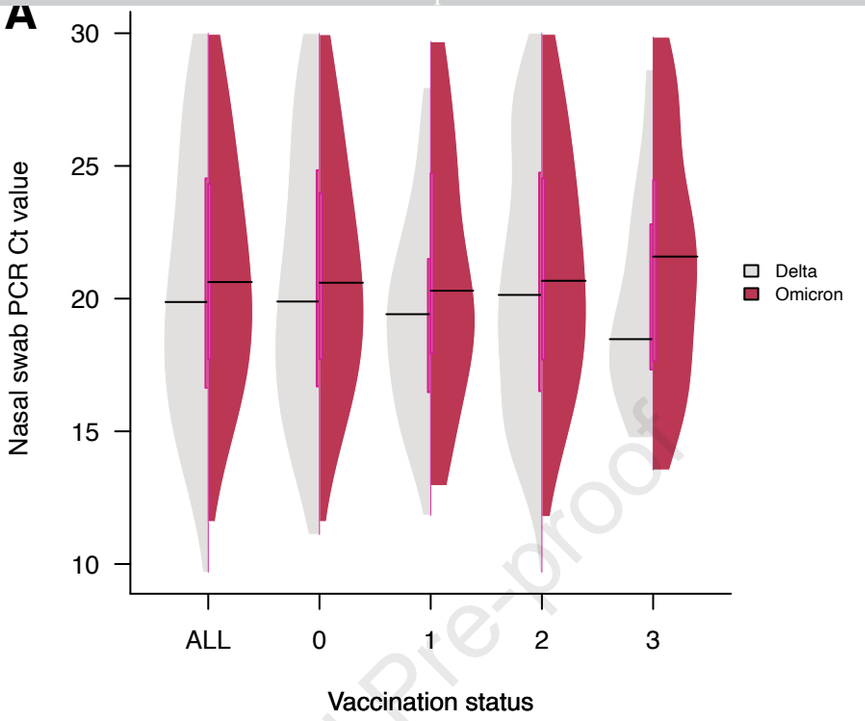
Highlights

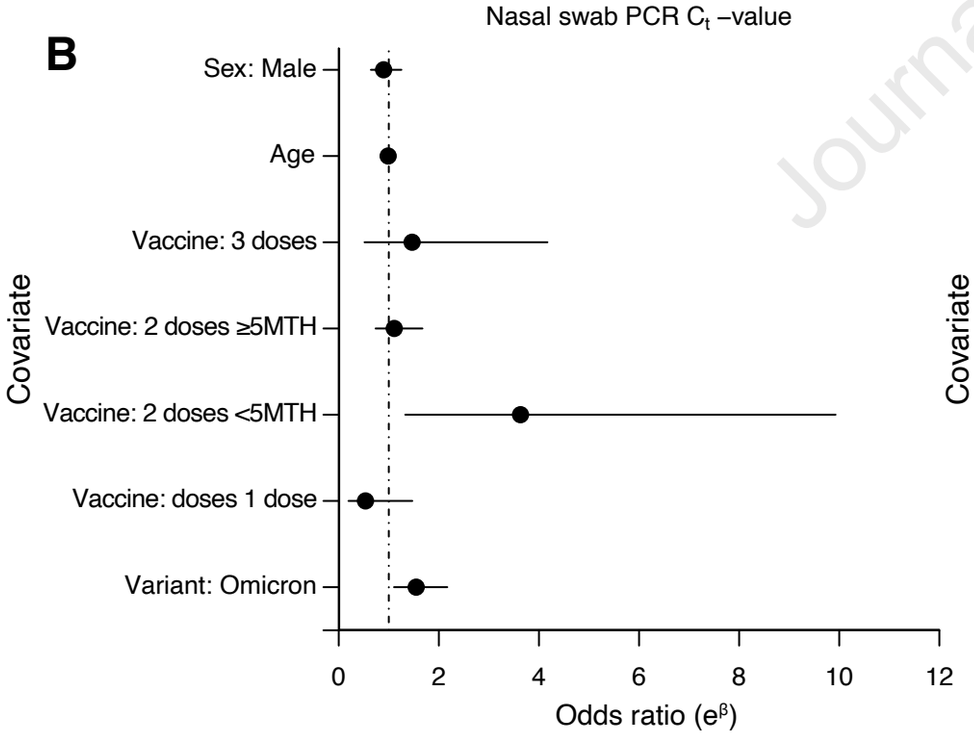
- Analysis of Delta and Omicron SARS-CoV-2 variants using nasal swab PCR samples
- Doubling time for Omicron ~4.3 times shorter than Delta variant
- Lower PCR test positivity rate for Delta and Omicron after three mRNA vaccine doses
- Higher odds of infection for Omicron than Delta variant in vaccinated individuals

In Brief

Chaguza et al. performed a cross-sectional study of nasal swab PCR test from a large hospital during a period of the equal prevalence of Delta and Omicron SARS-CoV-2 variants to compare the test positivity rates and effect of vaccination on the odds of infection with each variant.







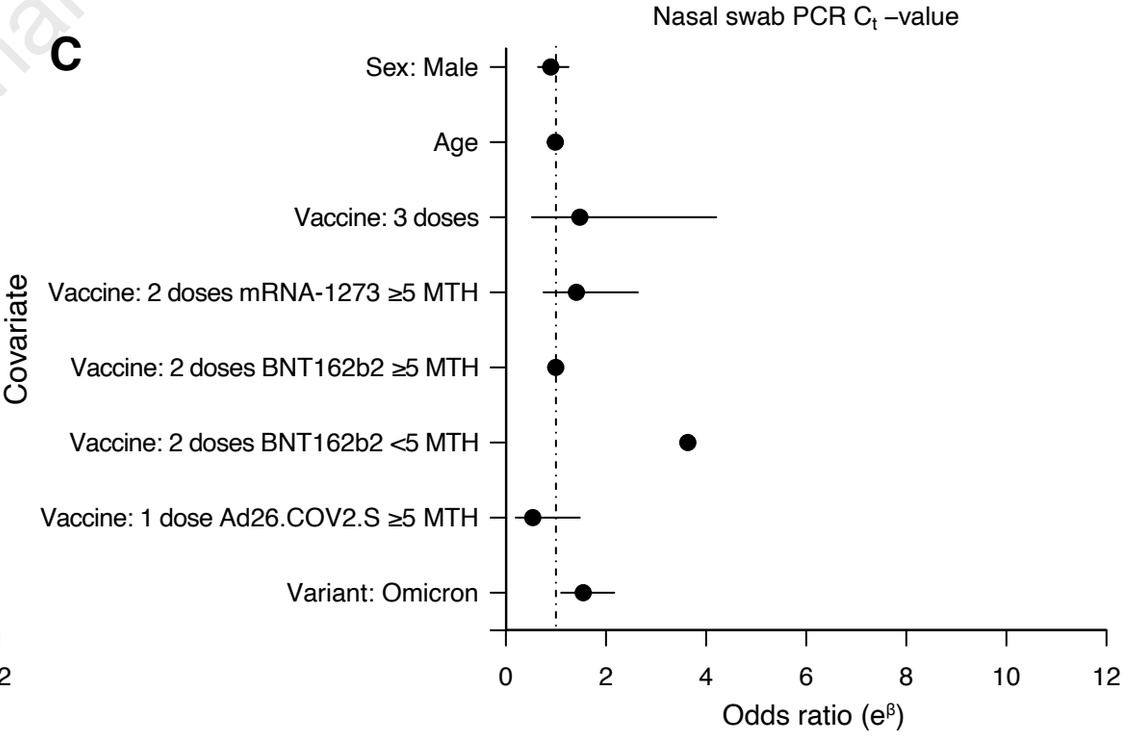


Table 1. Demographic characteristics among PCR tests performed between 12-26 December 2021.

	Number of vaccine doses			
Age group, y	0 (n=18072)	1 (n=1594)	2 (n=11537)	3 (n=2212)
0-5	2859 (15.82)	66 (4.14)	37 (0.32)	0 (0)
6-15	3921 (21.7)	424 (26.6)	930 (8.06)	1 (0.05)
16-30	3570 (19.75)	192 (12.05)	2033 (17.62)	162 (7.32)
31-45	3855 (21.33)	377 (23.65)	2953 (25.6)	508 (22.97)
46-60	2416 (13.37)	307 (19.26)	3009 (26.08)	626 (28.3)
>60	1451 (8.03)	228 (14.3)	2575 (22.32)	915 (41.37)
Sex				
Female	9842 (54.46)	847 (53.14)	6879 (59.63)	1398 (63.2)
Male	8219 (45.48)	747 (46.86)	4656 (40.36)	814 (36.8)
Unknown	11 (0.06)	0 (0)	2 (0.02)	0 (0)

Table 2. Positivity rates for Omicron and Delta among PCR tests performed between 12-26 December 2021.

Variant	All (Vaccinated & unvaccinated, n=33416)	0 dose – unvaccinated (n=17914)	Vaccinated – 1 dose (n=1405)	Vaccinated – 2 doses ≥5 months before test (n=1186)	Vaccinated – 2 doses <5 months before test (n=10322)	Vaccinated – 3 doses (n=2589)
Delta (Ct ≤ 30)	1374 (0.041: 0.039,0.043)	954 (0.053: 0.05,0.057)	57 (0.041: 0.03,0.051)	32 (0.027: 0.018,0.036)	306 (0.03: 0.026,0.033)	25 (0.01: 0.006,0.013)
Omicron (Ct ≤ 30)	1387 (0.042: 0.039,0.044)	793 (0.044: 0.041,0.047)	52 (0.037: 0.027,0.047)	58 (0.049: 0.037,0.061)	433 (0.042: 0.038,0.046)	51 (0.02: 0.014,0.025)
Negative or Ct > 30	30655 (0.917: 0.914,0.92)	16167 (0.902: 0.898,0.907)	1296 (0.922: 0.908,0.936)	1096 (0.924: 0.909,0.939)	9583 (0.928: 0.923,0.933)	2513 (0.971: 0.964,0.977)
Combined (Delta and Omicron)	2761 (0.083: 0.08,0.086)	1747 (0.098: 0.093,0.102)	109 (0.078: 0.064,0.092)	90 (0.076: 0.061,0.091)	739 (0.072: 0.067,0.077)	76 (0.029: 0.023,0.036)

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Confirmed COVID-19 cases	Yale New Haven Hospital	https://www.ynhh.org/
Estimated COVID-19 infections	Covidestim	https://covidestim.org/
Data and Software Availability		
R	RStudio	R version 4.0.3 https://cran.r-project.org/; https://www.rstudio.com/
Validation of spike gene target failure (SGTF) data	Mendeley Data	DOI: 10.17632/t3d3nd5wb9.1
Other		
SARS-CoV-2 variant frequencies	Yale University, Yale New Haven Hospital	https://github.com/grubaughlab/2022_paper_omicron-v-delta